REMARKS

Status of Claims

Claims 1, 3-25 and 27-33 are pending. The Examiner has withdrawn claims 7-25 and 27-28 from consideration as non-elected inventions. Claim 1 has been amended to define the abbreviations, "FIH" and "HIF". Claim 29 has been amended to correct spelling. Accordingly, Applicants have not introduced any new matter by the amendments.

Information Disclosure Statement

Applicants note that the Examiner's initials are missing for the five foreign patent documents, WO 01/90301 through WO 03/025013, cited on the PTO/SB/08 form filed April 15, 2005. The Examiner stated that the two Information Disclosure Statements filed by Applicants "have been considered as shown by the Examiner's initials next to each citation on the attached copy." Office Action at 3. Applicants respectfully request that the Examiner clarify the record to indicate that these five foreign patent documents were in fact considered by placing the Examiner's initials next to the documents.

Applicants also note that the Examiner marked that the date is missing for the U.K. Patent Office Search Report for Application No. GB 0224102.4. Applicants submit that the date for this report is March 14, 2003.

Compliance with Sequence Rules

The Examiner points to several instances where this application fails to fully comply with the requirements of 37 C.F.R § 1.821 through 1.825. Office Action at 3-4. Accordingly, Applicants have amended the specification to bring the application into compliance with the sequence rules.

Applicants submit the above amendment and attached Substitute Sequence Listing, and request amendment of the present specification by replacing the original Sequence Listing with the substitute Sequence Listing filed herewith. Applicants submit herewith a copy of the Sequence Listing in both CRF and paper form, as well as a Statement of Support that the content of the paper copy and the computer readable copy are the same. The specification has been amended to add the assignments of SEQ ID NOS 1-25.

Therefore, Applicants submit that this application is now fully compliant with the requirements of 37 C.F.R § 1.821 through 1.825.

Objections to the Specification

The Examiner objects to the title. Office Action at 5. Accordingly, the title has been amended according to the Examiner's suggestion.

The Examiner objects to the specification because it does not recite all of the SEQ ID NOS. As noted above, the specification has been amended to add the assignments of SEQ ID NOS 1-25.

Objections to the Claims

The Examiner objects to claim 29 reciting "co-ordinates." *Id.* The claim has been amended according to the Examiner's suggestion.

The Examiner objects that the use of abbreviations FIH and HIF should be spelled out on a first appearance in claims. *Id.* at 6. Claim 1 has been amended accordingly.

The Examiner objects to claims 1, 4-6, 29, 32 and 33, alleging that "it is unclear if FIH is used as a chemical entity or if the FIH is the hydroxylase." *Id.* The Examiner contends that "[t]he FIH is the hydroxylase according to claims 5 and 32." *Id.* Applicants respectfully submit that the claims are clear. Claims 5 and 32 refer to the inhibition of the asparaginyl hydroxylase

activity of FIH. It would be clear to one of ordinary skill in the art that these claims refer to a FIH which is capable of functioning as a hydroxylase. The specification is clear that, "[r]eferences to FIH herein refer to FIH and homologues thereof." Specification at page 4, line 25.

Rejection under 35 U.S.C. § 112, Second Paragraph

The Examiner rejects claims 6 and 33 under 35 U.S.C. § 112, Second Paragraph, for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. Office Action at 6. The Examiner contends that "[t]he position number used in the claim to describe specific amino acid residues of HIF is unclear without the point of reference, preferably identified by SEQ ID No." *Id.* Applicants respectfully traverse this rejection.

"The assays of the present invention may use . . . an asparagine containing substrate." Specification at page 21, lines 2-3. "Any suitable substrate in which an asparagine residue is hydroxylated by a FIH may be used." *Id.* at lines 8-9. "The asparagine equivalent to Asn 803 of HIF-1α may be determined by aligning the HIF variant, fragment or analogue to the sequence of HIF-1α to obtain the best sequence alignment and identifying thereby the asparagine equivalent to Asn 803 of HIF-1α." *Id.* at lines 17-20. The specification sufficiently describes the point of reference for the asparagine in fragments or homologues of HIF. Therefore, Applicants submit that the scope of these claims is clear.

Rejection under 35 U.S.C. § 112, First Paragraph

The Examiner rejects claims 1, 3-6 and 29-33 under under 35 U.S.C. § 112, First Paragraph, as allegedly failing to comply with the written description requirement.

The Examiner contends that "[t]he recited FIH is not defined by the instant specification; thus the instant FIH has been interpreted as any factor that inhibit[s] any protein or enzymes belonging to the same family as the HIF." Office Action at 8. The Examiner points to page 2 of the specification to reason that "instant FIH encompasses any protein, enzyme or polypeptide that inhibits enzymes belonging to the same family as HIF." *See id.* at 8-9. The Examiner then construes the instant claims to encompass a method comparing any structure model derived from a genus of factors inhibiting HIF with any chemical entity model structure having no structure limitation, wherein said structures are derived by X-ray crystallography of a FIH crystal. *See id.* at 9. The Examiner reasons that because protein crystallization is poorly understood, "a method of crystallization of a genus of FIH encompassed by the breadth of the claims is not adequately described by the method of crystallization disclosed in the specification and the prior art." *Id.* The Examiner then engages in an analysis of the factors to be considered in determining whether undue experimentation is required as summarized by *In re Wands* 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir., 1988). Office Action at 11-16. The Examiner concludes, at page 16 of the Office Action:

> In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required to make all methods and crystals as broadly encompassed by the claims, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention.

Applicants respectfully disagree and traverse this rejection.

The breadth of the claims: The Examiner bases his understanding of the breadth of the claims according to the specification at the middle of page 2. *See id.* at 12. However, the specification also emphasizes the need for selectivity for the intended target for the activation of

HIF, and that non-specific inhibition of just any enzymes which utilize dioxygen and 2OG, could lead toxic side effects. Specification at 2. Applicants submit that the Examiner has misread the specification to improperly broaden the definition of FIH to include all of the 2OG oxygenases mentioned in the specification at page 2. The prior art distinguishes FIH from other 2-OG oxygenases "FIH probably constitutes the first member of a new structural subfamily of 2-OG oxygenases." Hewitson at 26355. Therefore the Examiner's construction is overly broad.

In the present invention the HIF asparaginyl hydroxylase, FIH, has been crystallized. Furthermore, contrary to the Examiner's assertions, the specification adequately defines the term FIH. *See* Specification at page 4, line 1-31. "References to FIH herein refer to FIH and homologues thereof." Id. at line 25. The specification defines FIH, therefore this point of the rejection is improper.

Nature of the invention: The Examiner contends that the claimed method of using any model or any variation of FIH structure derived from the coordinates of Table 3, would be challenging to a skilled artisan given minor alterations could result in altered crystal forms or a lack of crystal growth. Office Action at 13. The specification states that "[t]he FIH may be a modified form." Specification at page 4, lines 19-20. And, "[t]ypically, when crystallised, a FIH mutant will adopt a similar 3-dimensional structure to that adopted by the corresponding FIH." *Id.* at lines 22-24. The specification properly defines the nature of the invention, therefore this point of the rejection is improper.

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: The Examiner cites various references which indicate that protein crystallization is unpredictable, and that alterations in the crystallization conditions can change the results.

Crystals were obtained for the structures 1-4 using similar crystallization conditions. *See* specification at page 39. "FIH and various fragments from seven to fifty-two residues were co-crystallised . . ." Id. at 37, line 17-18. The specification even mentions a limitation in the technique, that co-crystallization with CAD fragments shorter than twenty residues were not efficient. *Id.* at line 27. As a whole, the disclosure of the crystallization in the specification amounts to enough guidance to one skilled in the art to practice the invention. Therefore this point of the rejection is improper.

Amount of direction provided by the inventor; The existence of working examples: The Examiner recognizes that Table 2 lists many sequences belonging to the cupin structural superfamily including the instant genus FIH, yet states that "the chemical entity identified by the structure coordinates of Table 3 would not bind all cupin structural superfamily." Office Action at 15. Applicants submit that such an example would be beyond the scope of the claims. The present invention is directed to identifying, inter alia, a chemical entity which binds to FIH. Binding to FIH does not equal binding to all cupins.

The Examiner also alleges that "no single working example of [a] chemical entity identified by four structural coordinates in Table 3 is disclosed by the instant application." *Id.* at 15. Applicants disagree. At the very least, the structure coordinates identify that CAD binds to FIH. Therefore this point of the rejection is also improper.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: The Examiner alleges that "a skilled artisan is left to experiment . . . to determine whether the disclosed crystallization conditions . . . can be applied to the crystallization of other proteins or any protein within the genus FIH under a different set of crystallization parameters." *Id.* at 15-16. As noted above, as a whole, the disclosure of the

crystallization in the specification amounts to enough guidance to one skilled in the art to practice the invention as it relates to FIH and homologues thereof. Therefore this point of the rejection, too, is improper.

In view of the above remarks, Applicants respectfully submit that this rejection be withdrawn.

Rejection under 35 U.S.C. § 102

The Examiner rejects claims 1, 3, 5, 6, 29, and 31-33 under 35 U.S.C. § 102(b) as allegedly being anticipated by Hewitson et al. (May 31, 2002, The Journal of Biological Chemistry, vol. 149, pages 26351-55). Applicants respectfully disagree and traverse.

As an initial matter, Applicants respectfully submit that the rejection under 35 U.S.C. § 102(b) is improper because the Hewitson reference was not published more than one year prior to the priority date of the instant application. The Examiner has acknowledged "applicant's claim to foreign priority under 35 U.S.C. § 119(a) - (d) to foreign patent applications 0224102.4(filed on 10/16/2002, United Kingdom) and 0226598.1 (filed on 11/14/2002, United Kingdom) in English." Office Action at 3. The Hewitson reference, with a publication date of May 31, 2002, did not publish one year prior to either of these priority dates.

Furthermore, the disclosure of Hewitson also does not anticipate the present claims. A rejection under § 102 is proper only when the claimed subject matter is *identically described or disclosed* in the prior art. *In re Arkley*, 455 F.2d 586, 587 (C.C.P.A. 1972).

The Examiner improperly interprets the instant FIH as including any 2OG oxygenases identified on the basis of sequence analysis. The Examiner bases this rejection on "a very broad FIH." Office Action at 17. He then concludes that because Hewitson teaches a method

comprising comparing a structural model of phosphomannose isomerase (PMI) with zinc an inhibitor, the reference anticipates. *Id.* at 17-18.

Applicants have stated above that FIH is explicitly defined in the specification. Hewitson does not disclose a structural model of FIH required by the instant claims. Particularly, Hewitson does not disclose or suggest any crystal structure of FIH or the structural factors or coordinates obtained by subjecting a crystal of FIH to X-ray diffraction. For this reason, the cited reference does not anticipate or render obvious independent claim 1, independent claim 29, or any of the other pending claims which all depend from one of these two independent claims. Independent claim 1 specifies that the method "comprises comparing a structural model of FIH with a structural model for said chemical entity, wherein said structural model of FIH is derived from structural factors or structural coordinates determined by subjecting to X-ray diffraction measurements a crystal comprising FIH". As specified in independent claim 1, the structural model of FIH is derived from structural factors or structural coordinates determined by subjecting to X-ray diffraction measurements a crystal comprising FIH. Hewitson does not teach or suggest any structural model of FIH that is derived using the structural factors or structural coordinates determined by subjecting a crystal of FIH to X-ray diffraction. Therefore, the cited reference does not anticipate or render obvious claim 1 or claims 3, 4, 5, or 6 which depend from it. Independent claim 29 specifies that the method "comprises using the structural coordinates obtainable by subjecting a crystal comprising FIH to X-ray diffraction measurements and deducing the structural coordinates from the diffraction measurements." Again, Hewitson does not teach or suggest any structural coordinates that are obtainable or obtained by subjecting a crystal comprising FIH to X-ray diffraction measurements or deducing the structural coordinates from the diffraction measurements. Because Hewitson does not teach or suggest these features,

this reference does not anticipate or render obvious independent claim 29 or claims 30-33 which depend from this independent claim. Hewitson discloses structural models of PMI and clavaminic acid synthase (CAS1) to compare cores of 2OG oxygenases. Hewitson at 26355. However, it certainly does not disclose any crystal structure obtained from FIH or structural coordinates obtained therefrom. Therefore, this reference does not anticipate the claims of the present application, and does not include a sufficient enough amount of disclosure to enable one of ordinary skill in the art to identify, screen, characterize or design a chemical entity which mimics or binds to FIH, as recited in claims 1 and 29. The Examiner's construction is overly broad and the reference can not and does not anticipate any of the claims of the present application. For the reasons stated above, Applicants respectfully contend that each of the claims is novel in view of the cited reference and respectfully request that the Examiner reconsider and withdraw the rejection of these claims under § 102.

Rejection under 35 U.S.C. § 103

The Examiner rejects claims 3 and 30 under 35 U.S.C. § 103 as allegedly being unpatentable over Hewitson et al. in view of *In re Gulack* 703 F.2d 1381, 217 U.S.P.Q. 401 (Fed. Cir. 1983) and *In re Ngai* 367 F.3d 1336, 70 U.S.P.Q.2d 1862 (Fed. Cir. 2004). The Examiner contends that the data from Table 3 is nonfunctional descriptive material, because it does not change the function of the computer. Office Action at 20. The Examiner then concludes that it would have been obvious to employ the method as disclosed by Hewitson using any set of structural coordinates as defined in the claims with a reasonable expectation of success. *Id.* Applicants respectfully disagree and traverse the rejection.

Several basic factual inquires must be made to determine whether the claims of a patent application are obvious under 35 U.S.C. § 103. These factual inquiries, set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966), require the Examiner to:

(1) Determine the scope and content of the prior art;

(2) Ascertain the differences between the prior art and the claims in issue;

(3) Resolve the level of ordinary skill in the pertinent art; and

(4) Evaluate evidence of secondary considerations.

The obviousness or non-obviousness of the claimed invention is then evaluated in view of the results of these inquiries. *Graham*, 383 U.S. at 17-18, 148 USPQ 467; *see also KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 1734 (2007). The Federal Circuit has stated that "rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." M.P.E.P. § 2142 citing *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006). *See also KSR*, 127 S. Ct. at 1741, 82 USPQ2d at 1396 (quoting Federal Circuit statement with approval). Exemplary rationales that may support a conclusion of obviousness include, *inter alia*, choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success. M.P.E.P. § 2143 (emphasis added). "To reach a proper determination under 35 U.S.C. 103, the Examiner must step backward in time and into the shoes worn by the hypothetical "person of ordinary skill in the art" when the invention was unknown and just before it was made. In view of all factual information, the examiner must then make a determination whether the claimed invention "as a whole" would have been obvious at that time to that person." M.P.E.P. § 2142.

Applicants maintain that the Examiner has failed to satisfy the initial burden of establishing a prima facie case of obviousness. Applicants respectfully submit that the Examiner's allegation that a person of ordinary skill in the art at the time the invention was made would have employed the claimed method lacks merit.

As an initial matter, Hewitson does not render the present claims obvious. Hewitson discloses that a biological implication of the discovery of an additional regulator of HIF, which is also a member of the 2OG oxygenase family, and is distinct from the PHD isozymes, provides a further target for the development of therapeutic targets that augment HIF activity. Hewitson at 26353-54. Hewitson offers no identifiable, predictable solutions. As stated above, Hewitson does not teach one of ordinary skill in the art to identify, screen, characterize or design a chemical entity which mimics or binds to FIH, as recited in independent claims 1 and 29. Hewitson does not teach or suggest any structural model of FIH that is derived using the structural factors or structural coordinates determined by subjecting a crystal of FIH to X-ray diffraction. The Examiner's construction of FIH is overly broad. The assays and structural comparisons of 2OG oxygenases disclosed in Hewitson do not provide a structure of FIH or the structural coordinates obtained by subjecting a crystal of FIH to X-ray diffraction.

Gulack addresses "printed matter" rejections; "[w]here the printed matter is not functionally related to the substrate, the printed matter will not distinguish the invention from the prior art in terms of patentability." *Gulack*, 703 F.2d at 1385. *Ngai* held that because the instructions on an RNA extraction kit were not functionally related to the kit but merely taught a new use for an existing product, the claim drawn to the kit had been properly found to have been anticipated. *Ngai*, 367 F.3d at 1339. However, the Court also recognized that "Ngai can claim the new use as a method, but he cannot claim the existing product itself." *Id.* at 1338.

The instant claims are correctly directed to a method wherein the printed matter, the structural coordinates determined by x-ray diffraction measurements of a crystal comprising FIH, is functionally related to the method of identifying, screening, characterizing or designing chemical entities which bind to or mimic FIH. The Examiner's allegation that the structure coordinates are non-functional because they do not affect the performance of a computer are irrelevant.

For at least these reasons this rejection is improper and should be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, Applicant respectfully requests reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: December 19, 2007

By: _____
Mark D. Sweet
Reg. No. 41,469

Attachment: Marked up copy of Table 2

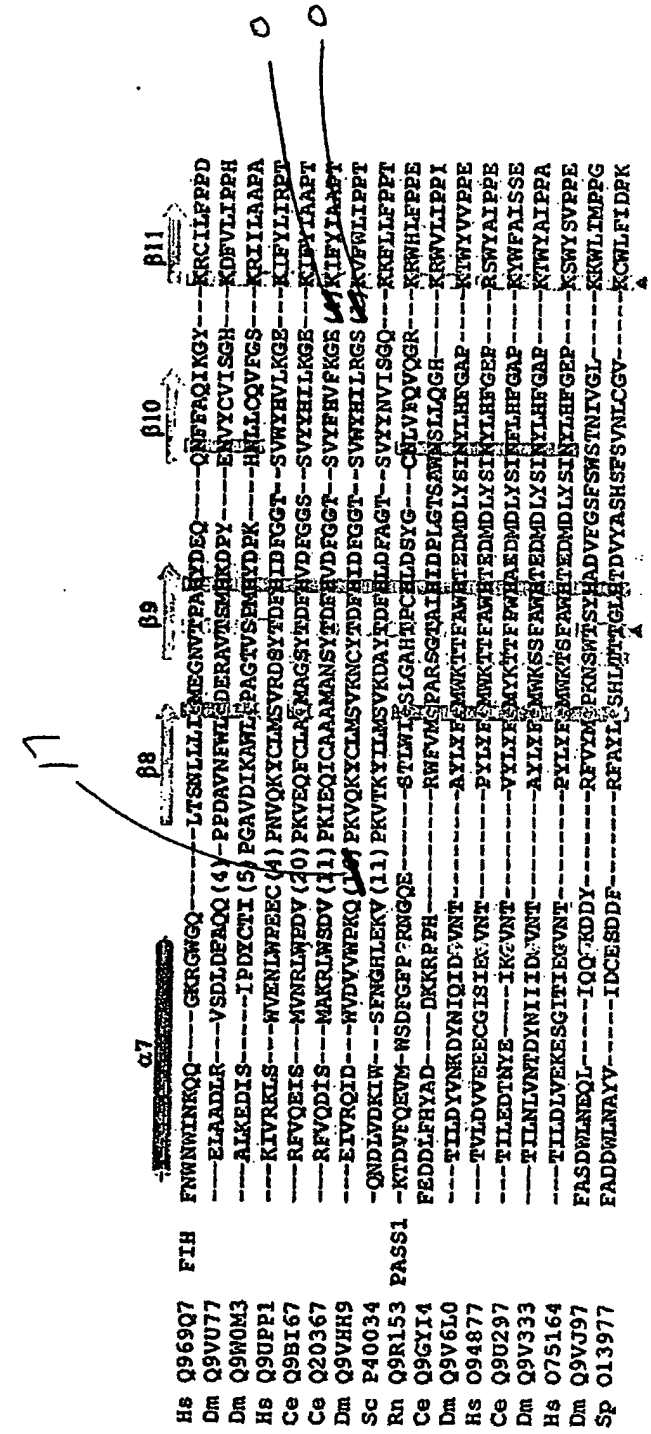
α7
β8
β9
β10
β11
Hs Q969Q7 FIH
Dm Q9VU77
Dm Q9W0M3
Hs Q9UPP1
Ce Q9BI67
Ce Q20367
Dm Q9VHH9
Sc P40034
Rn Q9R153 PASS1
Ce Q9GYI4
Dm Q9V6L0
Hs O94877
Ce Q9U297
Dm Q9V333
Hs O75164
Dm Q9VJ97
Sp O13977
Hs = Homo sapiens
Dm = Drosophila melanogaster
Ce = Caenorhabditis elegans
Sc = Saccharomyces cerevisiae
Rn = Rattus norvegicus
Sp = Schizosaccharomyces pombe
FIH = Factor Inhibiting HIF
PASS1 = Protein associating with small stress protein

TABLE 2